

REMARKS***Claim Amendments***

Claims 1-3, 5-14 and 16-17 have been amended, claim 4 has been cancelled, without prejudice, and replaced with new claim 18; and claim 15 has been cancelled and replaced with new claim 19. Following entry of these amendments, claims 1-3, 5-14 and 16-17 are pending in this application.

More specifically, claims 1, 2, 3 and 13 have been converted from “use” form to an appropriate method of use form, consistent with the method of original claim 17. Compound claim 4 has been cancelled and rewritten as self-contained compound claim 18, directly incorporating the appropriate compound formula (II) and the moiety definitions, which were indirectly incorporated by reference to claim 1 in original claim 4. Claims 1-12 have been amended to change their dependency from original claim 1 to replacement independent compound claim 18. Claims 14 and 16-17 have been amended to update their dependencies to refer to claims 18 and 5-12. Process for making claim 15 (originally dependent on “use” claim 1) has been rewritten as new claim 19, which is more appropriately dependent on the compound definition of claim 18 and related compound formula (II).

Support for all of these amendments is found in the original claims as filed, as well as throughout the specification, and no new matter has been added. Accordingly, entry of these amendments is believed to be in order, and entry of the same is respectfully requested.

Specification Amendment

An Abstract has been provided, typed on a separate page as requested by the Examiner. However, it should be recognized that this is a duplicate of the Abstract properly filed in the international application, and included with this application as filed. The purpose of the request for this duplicate Abstract is therefore not understood. The Examiner's attention is respectfully called to MPEP ¶1893.03(e), which provides in part:

Since applicant has already complied with PCT Rule 11.4 by filing the abstract on a separate sheet when the international application was filed, it is improper for the examiner of the U.S. national stage application to require an abstract on a separate sheet during national stage processing of the international application.

Claim Rejections – 35 USC § 112

Claims 1-3 and 13 have been rejected as being in an improper “use” format. These claims have been converted by the above amendments to a method of treatment format. Therefore, this ground for rejection has been overcome.

Claim 15 has been rejected as reciting “the limitation ‘R⁶²’ in formula I” on the ground that there is insufficient antecedent basis of this limitation in the claim. The basis for this rejection is not understood. In any event, claim 15 has been cancelled and replaced with new process claim 19. In process claim 19, subparagraph (d), R² is defined as R⁵X¹, wherein X¹ is as defined in claim 18, and R⁵ is C₁₋₅alkylR⁶², wherein R⁶² is selected from one of the nine groups that follow in claim 19. The group R⁶² is again used in formula (X) of claim 19, wherein R⁶² is “as defined herein”. Therefore, proper antecedent basis for the group R⁶²

appears throughout claim 19, and any basis there may have been for this rejection of claim 15 is not present in new claim 19.

Claim Objections

All objections with respect to improper multiple dependencies are believed to have been overcome by the above amendments to the claims.

Claim Rejections – 35 USC § 102

Claims 1 and 17 have been rejected under section 102(b) as being inherently anticipated by the Myers *et al.* reference. This ground for rejection is respectfully traversed, in view of the above claim amendments converting the “use” claims into an appropriate method of treatment form, and the following remarks. In particular, Myers *et al.* does not teach the method of treatment as presently claimed.

Myers *et al.* is not directed towards antiangiogenic agents, nor does it describe inhibitors of vascular endothelial growth factor (VEGF) receptor tyrosine kinase (RTK). Instead Myers *et al.*, page 3, lines 26-27, is directed to the inhibition of "CSF-1 and CSF-2 receptor signaling in bone remodeling and haematopoiesis". Myers *et al.*, page 3, lines 11-13, describes compounds which are "inhibitors of colony stimulating factor-1 receptor tyrosine kinase, CSF-1R, activity and have activity in a p56^{lck} cell-free assay." The compounds page 3, lines 15-16, "do not demonstrate significant PDGF-R activity in a cell-free assay" and, page 3, lines 23-24, "CSF-1R and PDGF-R (platelet derived growth factor receptor) are closely related." Furthermore the reference states at page 3, lines 25-26,

"compounds of this invention are selective inhibitors of CSF-1R tyrosine kinase activity" (emphasis added). It is suggested in Myers et al, page 3, lines 16-19, that the compounds therein may inhibit other src-like tyrosine kinases involved in the signal transduction pathway. However, it should be noted that VEGF RTK is not a src-like tyrosine kinase. VEGF RTK is a transmembrane RTK, unlike src which is an intracellular RTK. This means that VEGF RTK is a receptor tyrosine kinase and src is a non-receptor tyrosine kinase. VEGF RTK and src are in different families or RTK. The compounds of Myers *et al.* are said to be useful for the inhibition of cell proliferation and/or differentiation and/or mediator release by effectively inhibiting CSF-1R activity - see claim 1. Nowhere in Myers et al is there any mention of VEGF, its receptors, angiogenesis or vascular permeability.

Therefore, the method of treatment claimed in claims 1 and 17 of the present application is novel, and is not defined in Myers *et al.* Accordingly, this ground for rejection should be withdrawn.

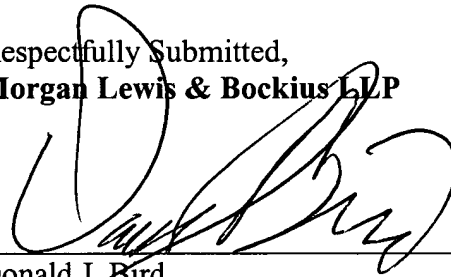
Information Disclosure Statement

The Examiner's attention is respectfully drawn to the Information Disclosure Statement filed herewith.

Conclusion

In view of the above amendments and the foregoing remarks, it is believed that all claims are in appropriate form and patentable over the record art. Accordingly, withdrawal of all grounds for rejection and the allowance of all claims are believed to be in order, and are respectfully requested.

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APPENDIX
VERSION WITH MARKINGS TO SHOW CHANGES

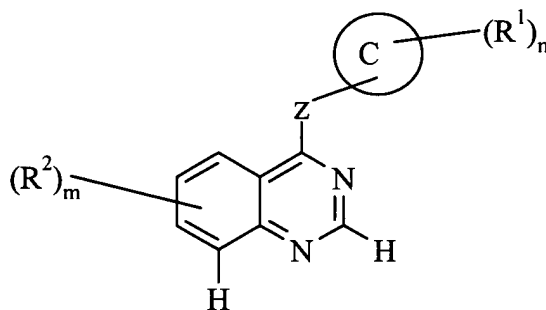
IN THE ABSTRACT:

A duplicate abstract has been presented on a separate page (per the Examiner's specific request), which is the same as the official abstract that was properly filed in the International Application and submitted with this application as filed.

IN THE CLAIMS:

Claims 1-3, 6-14 and 16-17 have been amended as follows, wherein added material is shown by **bold underlined text**, and deleted material is shown by **[bold text in brackets]**:

1. (Amended) [The use] **A method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need thereof, which comprises administering to said animal an effective amount** of a compound of the formula I:



wherein:

ring C is a 5-6-membered heterocyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which contains 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, -S- or -CH₂-;

R¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl, C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl, C₂₋₅alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphinyl, C₁₋₄alkylsulphonyl, carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl, C₁₋₄alkylsulphonylamino, C₁₋₄alkylamino, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄haloalkyl, C₁₋₄hydroxyalkoxy, carboxy and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C₁₋₄alkoxycarbonyl; and additionally R¹ may represent carboxy, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₃alkyl, or phenylC₂₋₄alkyl wherein the phenyl moiety may bear up to 5 substituents selected from the list herein defined for a phenyl ring which is directly linked to ring C;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

R² represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylsulphanyl, -NR³R⁴ (wherein R³ and R⁴, which may be the same or different, each represents hydrogen or C₁₋₃alkyl), or R⁵X¹- (wherein X¹ represents a direct

bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -SO-, -SO₂-, -NR⁶CO-, -CONR⁷-, -SO₂NR⁸-, -NR⁹SO₂- or -NR¹⁰- (wherein R⁶, R⁷, R⁸, R⁹ and R¹⁰ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and R⁵ is selected from one of the following eighteen groups:

- 1) hydrogen or C₁₋₅alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
- 2) C₁₋₅alkylX²COR¹¹ (wherein X² represents -O- or -NR¹²- (in which R¹² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹¹ represents C₁₋₃alkyl, -NR¹³R¹⁴ or -OR¹⁵ (wherein R¹³, R¹⁴ and R¹⁵ which may be the same or different each represents hydrogen, C₁₋₃alkyl, C₄₋₅alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 3) C₁₋₅alkylX³R¹⁶ (wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR¹⁷CO-, -CONR¹⁸-, -SO₂NR¹⁹-, -NR²⁰SO₂- or -NR²¹- (wherein R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁶ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄cyanoalkyl and C₁₋₄alkoxycarbonyl);
- 4) C₁₋₅alkylX⁴C₁₋₅alkylX⁵R²² (wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR²³CO-, -CONR²⁴-, -SO₂NR²⁵-, -NR²⁶SO₂- or -NR²⁷- (wherein R²³, R²⁴, R²⁵, R²⁶ and R²⁷ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);
- 5) R²⁸ (wherein R²⁸ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and C₁₋₄alkoxycarbonyl);

- 6) C₁₋₅alkylR²⁸ (wherein R²⁸ is as defined herein);
- 7) C₂₋₅alkenylR²⁸ (wherein R²⁸ is as defined herein);
- 8) C₂₋₅alkynylR²⁸ (wherein R²⁸ is as defined herein);
- 9) R²⁹ (wherein R²⁹ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -CONR³⁰R³¹ and -NR³²COR³³ (wherein R³⁰, R³¹, R³² and R³³, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 10) C₁₋₅alkylR²⁹ (wherein R²⁹ is as defined herein);
- 11) C₂₋₅alkenylR²⁹ (wherein R²⁹ is as defined herein);
- 12) C₂₋₅alkynylR²⁹ (wherein R²⁹ is as defined herein);
- 13) C₁₋₅alkylX⁶R²⁹ (wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR³⁴CO-, -CONR³⁵-, -SO₂NR³⁶-, -NR³⁷SO₂- or -NR³⁸- (wherein R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 14) C₂₋₅alkenylX⁷R²⁹ (wherein X⁷ represents -O-, -S-, -SO-, -SO₂-, -NR³⁹CO-, -CONR⁴⁰-, -SO₂NR⁴¹-, -NR⁴²SO₂- or -NR⁴³- (wherein R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 15) C₂₋₅alkynylX⁸R²⁹ (wherein X⁸ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁴CO-, -CONR⁴⁵-, -SO₂NR⁴⁶-, -NR⁴⁷SO₂- or -NR⁴⁸- (wherein R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷ and R⁴⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);
- 16) C₁₋₃alkylX⁹C₁₋₃alkylR²⁹ (wherein X⁹ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁹CO-, -CONR⁵⁰-, -SO₂NR⁵¹-, -NR⁵²SO₂- or -NR⁵³- (wherein R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each

independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁹ is as defined herein);

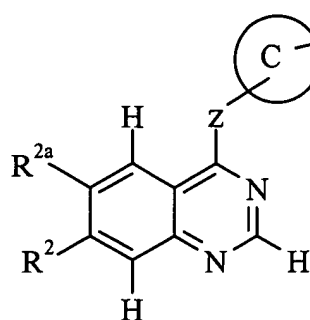
17) C₁₋₃alkylX⁹C₁₋₃alkylR²⁸ (wherein X⁹ and R²⁸ are as defined herein); and

18) C₁₋₃alkylR⁵⁴C₁₋₃alkylX⁹R⁵⁵ (wherein X⁹ is as defined herein and R⁵⁴ and R⁵⁵ are each independently selected from hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄cyanoalkyl and C₁₋₄alkoxycarbonyl), with the proviso that R⁵⁴ cannot be hydrogen;

and additionally wherein any C₁₋₅alkyl, C₂₋₅alkenyl or C₂₋₅alkynyl group in R⁵X¹- may bear one or more substituents selected from hydroxy, halogeno and amino;

or a **pharmaceutically acceptable** salt thereof [in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans].

2. (Amended) [The use] **A method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need thereof, which comprises administering to said animal an effective amount** of a compound of the formula Ia:



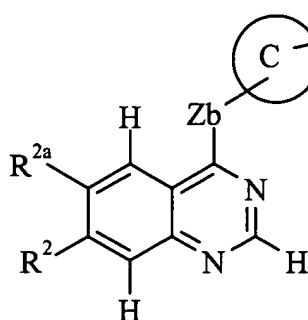
(Ia)

wherein:

ring C, R^1 , R^2 , n and Z are as defined in claim 1 with the proviso that R^2 is not hydrogen; and R^{2a} represents hydrogen, halogeno, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, $-NR^{3a}R^{4a}$ (wherein R^{3a} and R^{4a} , which may be the same or different, each represents hydrogen or C_{1-3} alkyl), or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein R^{5a} is a 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy, za is an integer from 0 to 4 and X^{1a} represents a direct bond, $-O-$, $-CH_2-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{6a}CO-$, $-CONR^{7a}-$, $-SO_2NR^{8a}-$, $-NR^{9a}SO_2-$ or $-NR^{10a}-$ (wherein R^{6a} , R^{7a} , R^{8a} , R^{9a} and R^{10a} each independently represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));

or a **pharmaceutically acceptable salt thereof**, **in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans**].

3. (Amended) [The use] **A method for producing an antiangiogenic or vascular permeability reducing effect in a warm-blooded animal in need thereof, which comprises administering to said animal an affective amount** of a compound of the formula Ib:



(Ib)

wherein:

ring C, R^1 , R^2 and n are as defined in claim 1 with the proviso that R^2 is not hydrogen, R^{2a} is as defined in claim 2; and

Zb is -O- or -S-;

or a **pharmaceutically acceptable** salt thereof], **in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans**].

5. (Amended) A compound as claimed in claim 18 [4] wherein Zb is -O-.

6. (Amended) A compound as claimed in claim 18 [4 or claim 5] wherein R^{2a} is methoxy.

7. (Amended) A compound as claimed in claim 18 [any one of claims 4-6] wherein ring C is a 5-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

8. (Amended) A compound as claimed in claim 18 [any one of claims 4-7] wherein R^1 is a phenyl group or a 5-6-membered heteroaromatic group with 1-3 heteroatoms, selected independently from O, S and N, (linked via a ring carbon atom), which phenyl or heteroaromatic group is optionally substituted as defined in claim 18 [1].

9. (Amended) A compound as claimed in claim 18 [any one of claims 4-8] wherein

R^2 represents hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3} alkyl, cyano, amino or R^5X^1 -

[[wherein X^1 is as defined in claim 18 [1] and R^5 is selected from one of the following eighteen groups:

- 1) C_{1-4} alkyl which may be unsubstituted or substituted with one or more fluorine atoms, or C_{2-4} alkyl which may be unsubstituted or substituted with 1 or 2 groups selected from hydroxy and amino;
- 2) C_{2-3} alkyl X^2COR^{11} (wherein X^2 is as defined in claim 18 [1] and R^{11} represents $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13} , R^{14} and R^{15} which may be the same or different are each C_{1-2} alkyl or C_{1-2} alkoxyethyl));
- 3) C_{2-4} alkyl X^3R^{16} (wherein X^3 is as defined in claim 18 [1] and R^{16} is a group selected from C_{1-3} alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl and piperidinyl which group is linked to X^3 through a carbon atom and which C_{1-3} alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-2} alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl or piperidinyl group may carry one substituent selected from oxo, hydroxy, halogeno, C_{1-2} alkyl, C_{1-2} hydroxyalkyl and C_{1-2} alkoxy);
- 4) C_{2-3} alkyl X^4C_{2-3} alkyl X^5R^{22} (wherein X^4 and X^5 are as defined in claim 18 [1] and R^{22} represents hydrogen or C_{1-3} alkyl);
- 5) C_{1-4} alkyl R^{59} (wherein R^{59} is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to C_{1-4} alkyl through a carbon atom and which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-2} alkoxy C_{1-3} alkyl and C_{1-2} alkylsulphonyl C_{1-3} alkyl) or C_{2-4} alkyl R^{60} (wherein R^{60} is a group selected from morpholino, thiomorpholino, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may carry 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-2} alkoxy C_{1-3} alkyl and C_{1-2} alkylsulphonyl C_{1-3} alkyl);
- 6) C_{3-4} alkenyl R^{61} (wherein R^{61} represents R^{59} or R^{60} as defined herein);
- 7) C_{3-4} alkynyl R^{61} (wherein R^{61} represents R^{59} or R^{60} as defined herein);
- 8) R^{29} (wherein R^{29} is as defined in claim 18 [1]);

- 9) $C_{1-4}alkylR^{29}$ (wherein R^{29} is as defined in claim **18** [1]);
 - 10) $1-R^{29}prop-1-en-3-yl$ or $1-R^{29}but-2-en-4-yl$ (wherein R^{29} is as defined in claim **18** [1] with the proviso that when R^5 is $1-R^{29}prop-1-en-3-yl$, R^{29} is linked to the alkenyl group via a carbon atom);
 - 11) $1-R^{29}prop-1-yn-3-yl$ or $1-R^{29}but-2-yn-4-yl$ (wherein R^{29} is as defined in claim **18** [1] with the proviso that when R^5 is $1-R^{29}prop-1-yn-3-yl$, R^{29} is linked to the alkynyl group via a carbon atom);
 - 12) $C_{1-5}alkylX^6R^{29}$ (wherein X^6 and R^{29} are as defined in claim **18** [1]);
 - 13) $1-(R^{29}X^7)but-2-en-4-yl$ (wherein X^7 and R^{29} are as defined in claim **18** [1]);
 - 14) $1-(R^{29}X^8)but-2-yn-4-yl$ (wherein X^8 and R^{29} are as defined in claim **18** [1]);
 - 15) $C_{2-3}alkylX^9C_{1-2}alkylR^{29}$ (wherein X^9 and R^{29} are as defined in claim **18** [1]);
 - 16) R^{28} (wherein R^{28} is as defined in claim **18** [1]);
 - 17) $C_{2-3}alkylX^9C_{1-2}alkylR^{28}$ (wherein X^9 and R^{28} are as defined in claim **18** [1]); and
 - 18) $C_{2-3}alkylR^{54}C_{1-2}alkylX^9R^{55}$ (wherein X^9 , R^{54} and R^{55} are as defined in claim **18** [1]);
- and additionally wherein any $C_{1-5}alkyl$, $C_{2-5}alkenyl$ or $C_{2-5}alkynyl$ group in R^5X^1 - may bear one or more substituents selected from hydroxy, halogeno and amino[[]].

10. (Amended) A compound as claimed in **claim 18** [any one of claims 4-9] wherein R^2 represents 2-methoxyethoxy, 2-(2-methoxyethoxy)ethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(tetrahydropyran-4-yloxy)ethoxy, 3-(tetrahydropyran-4-yloxy)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy 2-(1,1-dioxothiomorpholino)ethoxy, 3-(1,1-dioxothiomorpholino)propoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(N-methoxyacetyl-N-methylamino)ethoxy, 3-(N-methoxyacetyl-N-methylamino)propoxy, N-methylpiperidin-3-ylmethoxy, 4-(pyrrolidin-1-yl)but-2-en-yloxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 3-(2-oxopyrrolidin-1-yl)propoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(2-(pyrrolidin-1-yl)ethoxy)ethoxy, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy,

2-piperidinoethoxy, 3-piperidinopropoxy, 2-(methylpiperidino)ethoxy,
3-(methylpiperidino)propoxy, 2-(ethylpiperidino)ethoxy, 3-(ethylpiperidino)propoxy,
2-((2-methoxyethyl)piperidino)ethoxy, 3-((2-methoxyethyl)piperidino)propoxy,
2-((2-methylsulphonyl)ethylpiperidino)ethoxy,
3-((2-methylsulphonyl)ethylpiperidino)propoxy, piperidin-3-ylmethoxy,
piperidin-4-ylmethoxy, 2-(piperidin-3-yl)ethoxy, 2-(piperidin-4-yl)ethoxy,
3-(piperidin-3-yl)propoxy, 3-(piperidin-4-yl)propoxy, 2-(methylpiperidin-3-yl)ethoxy,
2-(methylpiperidin-4-yl)ethoxy, 3-(methylpiperidin-3-yl)propoxy,
3-(methylpiperidin-4-yl)propoxy, 2-(ethylpiperidin-3-yl)ethoxy,
2-(ethylpiperidin-4-yl)ethoxy, 3-(ethylpiperidin-3-yl)propoxy,
3-(ethylpiperidin-4-yl)propoxy, 2-((2-methoxyethyl)piperidin-3-yl)ethoxy,
2-((2-methoxyethyl)piperidin-4-yl)ethoxy, 3-((2-methoxyethyl)piperidin-3-yl)propoxy,
3-((2-methoxyethyl)piperidin-4-yl)propoxy,
2-((2-methylsulphonylethyl)piperidin-3-yl)ethoxy,
2-((2-methylsulphonylethyl)piperidin-4-yl)ethoxy,
3-((2-methylsulphonylethyl)piperidin-3-yl)propoxy,
3-((2-methylsulphonylethyl)piperidin-4-yl)propoxy, 1-isopropylpiperidin-2-ylmethyl,
1-isopropylpiperidin-3-ylmethyl, 1-isopropylpiperidin-4-ylmethyl,
2-(1-isopropylpiperidin-2-yl)ethyl, 2-(1-isopropylpiperidin-3-yl)ethyl,
2-(1-isopropylpiperidin-4-yl)ethyl, 3-(1-isopropylpiperidin-2-yl)propyl,
3-(1-isopropylpiperidin-3-yl)propyl, 3-(1-isopropylpiperidin-4-yl)propyl,
3-(4-methylpiperazin-1-yl)propoxy, 1-methylpiperidin-4-ylmethoxy,
1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy,
1-(2-pyrrolidinylethyl)piperidin-4-ylmethoxy,
1-(3-pyrrolidinylpropyl)piperidin-4-ylmethoxy, 1-(2-piperidinylethyl)piperidin-4-ylmethoxy,
1-(3-piperidinylpropyl)piperidin-4-ylmethoxy, 1-(2-morpholinoethyl)piperidin-4-ylmethoxy,
1-(3-morpholinopropyl)piperidin-4-ylmethoxy,
1-(2-thiomorpholinoethyl)piperidin-4-ylmethoxy,

1-(3-thiomorpholinopropyl)piperidin-4-ylmethoxy,
1-(2-azetidinyethyl)piperidin-4-ylmethoxy or 1-(3-azetidinypropyl)piperidin-4-ylmethoxy.

11. (Amended) A compound as claimed in claim **18 [4]** selected from:

4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-quinazoline,
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)-propoxy)quinazoline,
6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(3-furyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(4-chlorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(5-phenylpyrazol-3-yloxy)-quinazoline,
6-methoxy-7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(2-(1,2,3-triazol-1-yl)ethoxy)-quinazoline and
4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)-6-methoxy-7-(1-(2-methylsulphonyl)ethyl)-piperidin-4-ylmethoxy)quinazoline,
and salts thereof.

12. (Amended) A compound as claimed in claim **18 [4]** selected from:

7-(2-methoxyethoxy)-4-(5-phenylpyrazol-3-yloxy)quinazoline,
4-(5-(2-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(3-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-nitrophenyl)pyrazol-3-yloxy)quinazoline,
6-methoxy-7-(3-morpholinopropoxy)-4-(5-(4-pyridyl)pyrazol-3-yloxy)quinazoline,
4-(5-(4-fluorophenyl)pyrazol-3-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline, and
6-methoxy-7-(2-methoxyethoxy)-4-(5-(4-methoxyphenyl)pyrazol-3-yloxy)quinazoline,

and salts thereof.

13. (Amended) [The use of a compound] **The method** as claimed in claim 1 **wherein the compound is** selected from:

6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(5-phenylpyrazol-3-ylamino)-quinazoline

and

6,7-dimethoxy-4-(5-phenylpyrazol-3-yloxy)quinazoline

and pharmaceutically acceptable salts [or a salt] thereof[, **in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans**].

14. (Amended) A compound as claimed in any one of claims [4] **18 and 5** to 12 in the form of a pharmaceutically acceptable salt.

16. (Amended) A pharmaceutical composition which comprises as active ingredient a compound of formula **II [I]** or a pharmaceutically acceptable salt thereof as claimed in any one of claims [4] **18 and 5** to 12 in association with a pharmaceutically acceptable excipient or carrier.

17. (Amended) A method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **II [I]** as defined in **any one of claims 18 and 5 to 12 [claim 1]** or a pharmaceutically acceptable salt thereof.

Claim 4 has been cancelled and replaced with new claim 18.

Claim 15 has been cancelled and replaced with new claim 19.